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(54) Title: DRY FORMULATION FOR TRANSCUTANEOUS IMMUNIZATION

(57) Abstract

A transcutaneous immunization system delivers antigen to immune cells through the skin, and induces an immune response in an animal or human. For example, a skin-active adjuvant (e.g., an ADP-ribosylating exotoxin) can be used to induce an antigen-specific immune response (e.g., humoral and/or cellular effectors) after transcutaneous application of a dry formulation containing antigen and adjuvant to skin of the animal or human. The dry formulation may be a powder or a unit-dose patch. Use of adjuvant is not required if the antigen is sufficiently antigenic. Transcutaneous immunization may be induced with or without penetration enhancement.

We Claim:

1. Formulation for transcutaneous immunization comprised one or more antigen and adjuvant ingredients, wherein at least one of the ingredients is in dry form, and whereby application of the formulation to intact skin induces an immune response specific for the antigen.

2. Formulation according to Claim 1, wherein at least one adjuvant is an ADP-ribosylating exotoxin.

3. Formulation according to Claim 1, wherein at least one adjuvant is selected from the group consisting of unmethylated CpG dinucleotides, lipopolysaccarides, and cytokines.

4. Formulation according to Claim 1, wherein at least one adjuvant is provided in the formulation as a nucleic acid.

5. Formulation according to Claim 4, wherein the nucleic acid further contains a regulatory region operably linked to a sequence encoding an adjuvant.

6. Formulation according to Claim 4, wherein the nucleic acid is a non-integrating and non-infectious plasmid.

7. Formulation according to Claim 1, wherein at least one antigen has a molecular weight greater than 500 daltons.

8. Formulation according to Claim 1, wherein at least one antigen is derived from a pathogen selected from the group consisting of bacterium, virus, fungus, and parasite.

9. Formulation according to Claim 1, wherein at least one antigen is a tumor antigen or an autoantigen.

10. Formulation according to Claim 1, wherein at least one antigen is selected from the group consisting of carbohydrate, glycolipid, glycoprotein, lipid, lipoprotein, phospholipid, and polypeptide.

11. Formulation according to Claim 1, wherein the formulation is comprised of an attenuated live virus and at least one antigen is expressed by the attenuated live virus.

12. Formulation according to Claim 1, wherein at least one antigen is a polypeptide of greater than 500 daltons molecular weight.

13. Formulation according to Claim 1, wherein at least one antigen is multivalent.

14. Formulation according to Claim 1, wherein at least one antigen is provided in the formulation as a nucleic acid encoding a polypeptide.

15. Formulation according to Claim 14, wherein the nucleic acid is a non-integrating and non-infectious plasmid.

16. Formulation according to Claim 1, wherein a single molecule is both an adjuvant and an antigen of the formulation.

17. Formulation according to any one of Claims 1-16, wherein the formulation does not include a penetration enhancer, viral particle, liposome, or charged lipid.

18. Formulation according to any one of Claims 1-16, wherein the formulation does include a chemical penetration enhancer that increases effectiveness of immunization in comparison to use of a formulation lacking the chemical penetration enhancer.

19. Formulation according to any of Claims 1-18, wherein an antigen and an adjuvant are both provided in dry form in the formulation.

20. Formulation according to any of Claims 1-18, wherein at least one adjuvant is provided in dry form.

21. Formulation according to any of Claims 1-18, wherein at least one antigen is provided in dry form.

22. Formulation according to any of Claims 1-21, whereby exposure of the intact skin to the adjuvant activates an underlying Langerhans cell.

23. Formulation according to any of Claims 1-21, whereby exposure of the intact skin to the adjuvant causes an underlying Langerhans cell to increase major histocompatibility complex class II expression.

24. Formulation according to any of Claims 1-21, whereby exposure of the intact skin to the adjuvant causes migration of an underlying Langerhans cell to a lymph node.

25. Formulation according to any of Claims 1-21, whereby exposure of the intact skin to the adjuvant signals an underlying Langerhans cell to mature into an antigen presenting cell.

26. Formulation according to any of Claims 1-21, whereby exposure of the intact skin to the adjuvant enhances antigen presentation to lymphocytes.

27. Formulation according to any of Claims 1-26 further comprising applying alcohol to the intact skin prior to application of the formulation.

28. Formulation according to any of Claims 1-26 further comprising hydrating the intact skin prior to application of the formulation.

29. Formulation according to any of Claims 1-26 further comprising dissolving at least one dry ingredient of the formulation during or after application of the formulation such that a saturated solution of that ingredient is placed in contact with the intact skin.

30. Formulation according to Claim 29, wherein the formulation is further comprised of an immunologically-inactive polymer that reduces the dissolved ingredient's concentration in a saturated solution.

31. Formulation according to any of Claims 1-30 further comprising a dressing and thereby providing a patch form of the formulation.

32. Formulation according to Claim 31, wherein the dressing is an occlusive dressing.

33. Formulation according to Claim 31, wherein the intact skin covered by the dressing has a surface area which is larger than at least one draining lymph node field.

34. Use of a dry formulation for transcutaneous immunization comprising applying a formulation to skin of a subject under conditions that induce an immune response to at least one antigen of the formulation.

35. Use according to Claims 34, wherein application of the formulation occurs to intact skin without perforation thereof.

36. Use according to Claims 34 further comprising enhancing penetration of at least one antigen or adjuvant through the skin with at least one physical or chemical penetration enhancer applied to the skin before, after and/or during application of the formulation to the skin.

37. Production of a dry formulation for transcutaneous immunization comprising in any order:

(a) providing at least one immunolgically-active ingredient, wherein the formulation contains at least one immunolgically-active ingredient with antigen activty;

(b) dissolving at least one of the immunologically-active ingredients to produce an immunologically-active liquid;

(c) drying the immunologically-active liquid on a solid substrate; and

(d) combining immunologically-active ingredients together to produce the formulation; wherein at least one of the immunologically-active ingredients is in dry form at least until the formulation is applied to skin of a subject to be immunized.

38. Production according to Claim 37, further comprising mixing all active ingredients together to produce a homogeneous formulation.

39. Production according to any of Claims 37-38, wherein the formulation is comprised essentially of one immunologically-active ingredient.

40. Production according to any of Claims 37-39, wherein the solid substrate is a dressing and the formulation is thereby provided as a patch.

41. Production according to any of Claims 37-40, wherein the formulation is produced under aseptic conditions suitable for production of a vaccine.

42. Production according to any of Claims 37-41, wherein a single application of the formulation is sufficient to induce a detectable antigen-specific immune response.

43. Production according to any of Claims 37-42, wherein the formulation is further comprised of at least one excipient, stabilizer, dessicant, or preservative.

44. Production according to any of Claims 37-43, wherein the formulation is further comprised of at least one immunologically-inactive polymer that reduces the dissolved ingredient's concentration in a saturated solution.